REMARKS

The applicants express appreciation to the Examiner for consideration of the subject patent application. This amendment is in response to the Office Action mailed March 07, 2006. Claims 1-27 are pending in the application. Claims 1, 4, 6, 8, 15, 18, and 27 were objected to. Claims 4, 9, 10, 15, 16, 19, and 27 were rejected under 35 U.S.C.112, and claims 12-21, 24 and 25 were rejected under 35 U.S.C.103. The claims have been amended to address the concerns raised by the Examiner's objections. No new matter is added through the amendment.

Claim Rejections - 35 U.S.C. § 112

Claims 4, 9, 10, 15, 16, 19, 20 and 27 are rejected under § 112, 2nd paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which the applicants regard as the invention. The claims have been amended to address the concerns raised by the Examiner.

Claim Rejections - 35 U.S.C. § 103

Claims 12-21, 24, and 25 are rejected under USC 103(a) as being unpatentable over Epand et al., US 5,283,185 in view of Ogris et al., (Gene therapy(1990)6:595-605).

Claims 12-15, 17-21, 24 and 25 are rejected under USC 103(a) as being unpatentable over Epand et al., US 5,283,185 in view of Godbey et al.,(J.Contr.Rel.(1999)60:149-160).

In order to most succinctly explain why the claims presented herein are allowable, the Applicants will direct the following remarks primarily to the originally presented independent Claim 12, with the understanding that once an independent claim is allowable, all claims depending therefrom are allowable.

The applicants respectfully submit that the presently amended claims are not obvious in view of the references cited. In other words, one of ordinary skill in the art, when considering all of the

teachings of each reference, either singly or in combination at the time the invention was made, would not have been motivated to come up with the presently claimed invention.

The burden is on the Examiner to establish a case of *prima facie* obviousness. *In re Fine*, 5 U.S.P.Q.2d 1596, 1598 (Fed. Cir.1988). When making a rejection under 35 U.S.C. § 103 there are three fundamental areas the Examiner is required, under 37 C.F.R. § 1.106 and MPEP § 706.02, to cover. First, the rejection should set forth the differences between the claims and the prior art. Second, the proposed modification of the applied references necessary to arrive at the claimed subject matter should be clearly stated. Third, there must be an explanation as to why such proposed modifications would be obvious.

The real issue under § 103 is whether the Examiner has stated a case of *prima facie* obviousness. The test for establishing such a case is well stated in *In re Lintner*, 173 USPQ 560, 562 (CCPA 1972) as follows:

> "In determining the propriety of the Patent Office case for obviousness in the first instance, it is necessary to ascertain whether or not the reference teaching would appear to be sufficient for one of ordinary skill in the relevant art having the reference before him to make the proposed substitution, combination or other modification."

Under this statement of law, the Applicants respectfully submit that the present invention would not be obvious over the cited references.

The present application relates to novel lipopolymer compositions and the complexes they formed with DNA for gene delivery. These lipopolymers comprise polyethylenimine (PEI), a lipid and a biocompatible hydrophilic polymer, wherein the lipid and the biocompatible hydrophilic polymer are directly and independently attached to the PEI backbone by covalent bonds. These lipopolymer compositions further comprise a targeting moiety, which is covalently attached to the

PEI backbone directly or through a hydrophilic spacer. The Examiner alleges that claims (12,18,24,25) are obvious in light of the combined teachings of Epand et al., (PEI coupled to cholesterol) and Ogris et. al., (PEI coupled with polyethylene glycol (PEG)).

The Applicants respectfully disagree and argue that both the composition and method of synthesis of the lipopolymers described in the present application (claims 12 and 18) and their complexes with DNA (claims 24 and 25) would not be obvious from the cited references. The lipopolymer composition of the present invention, its synthesis (Fig. 1), analytical characteristics (Figs. 2-5) and gene transfer utility (Figs. 6-8) have not been taught or suggested in the cited references.

The method of PEI coupling to cholesterol and PEG in the current application (Fig. 1 and Examples 1-3, 8-10) is significantly different from that of the cited methods for PEI coupling to cholesterol (Epand's et al., Example XV) and to PEG (Ogris et al., page 602). The novel polymer compositions of the present invention are synthesized with a one-pot reaction scheme where PEI, cholesterol chloroformate and PEG are reacted simultaneously. Epand and Ogris do not teach this reaction scheme. As acknowledged by the Examiner (Office Action, page 4, 3rd paragraph), Epand et al., does not teach DNA complexation with a lipopolymer which is covalently modified with a biocompatible hydrophilic polymer. Epand's compound comprises only cholesterol chloroformate and PEI 600. Orgis teaches PEGylation of PEI which is covalently linked to transferrin and is already complexed with DNA (DNA/PEI-transferrin). Our invention teaches PEGylation of unbound or free PEI. The inherent heterogeneity of DNA/PEI complexes is characterized by broad size distribution of the complexes and variance in the conformation of interacting molecules on the particle surface would make it highly challenging to control the efficiency and reproducibility of

PEI:PEGylation. Since the degree of PEG incorporation in the PEGylated product was not quantified their final product and its true characteristics with respect to PEG incorporation is obscure. Therefore, one skilled in the art would not be motivated to combine Orgis with Epand to produce the presently claimed novel lipopolymer composition.

Combined teachings of Epand and Ogris would suggest a sequential approach where PEI is first reacted with cholesterol (Epand et al.,) and the resultant PEI-cholesterol product is then complexed with DNA before reaction with PEG (Ogris et al.), or vice versa. There is no direct structural proof of PEGylation in Orgis' claim. Their biological data is confounding where PEGylation appeared to have improved pharmacokinetics but failed to preclude particle aggregation and in vivo toxicity under specific conditions. The lipopolymer described in our invention is fully characterized by structural composition and biological activity and the corresponding method teaches to control the degree of PEGylation to obtain different biological activity (Fig. 7 of present invention). The synthesis scheme described in Applicants application is both conceptually and procedurally different and non-obvious from the cited references. Therefore, one skilled in the art would not be motivated to combine Epand with Orgis to produce lipopolymers comprised of polyethylenimine (PEI), a lipid and a biocompatible hydrophilic polymer, wherein the lipid and the biocompatible hydrophilic polymer are directly and independently attached to the PEI backbone by covalent bonds, as claimed in the present invention. In the following paragraph, an argument is made as to why Orgis' method could not teach the material described in the present invention.

A significant population of the PEI primary amines in Orgis' DNA/PEI-transferrin conglomerate would be bound to the negatively charged DNA phosphate and shielded by the large transferrin ligand. Under these reaction conditions, not only there is limited accessibility of free

primary amines in DNA/PEI-transferrin conglomerate to the PEG reagent there is also impracticality of assessing the density of such free amines. This makes it highly challenging to calculate the amount of reactant PEG needed to achieve a desired amount of PEG incorporation per PEI molecule. Orgis uses a ninhydrin assay to calculate the number of free amines occupied by the PEG reagent to assess the degree of PEG incorporation. However, there is no data to support their claim. On page 603, line 18, Orgis states that "the ninhydrin assay was found to give the same results with free or DNA bound PEI conjugates," which suggests DNA complexation did not affect the number of free amines which itself contradicts the basis of DNA and PEI interaction. At N/P ratio 6, a considerable number of PEI primary amines should be bound to DNA phosphate and hence would be inaccessible to the PEG reagent. This discrepancy questions the validity of PEGylation scheme and in the absence of any supporting structural information doubts the composition of the end product. The ninhydrin assay used to quantify the degree of PEI PEGylation in DNA complexes is non-conventional and subject to criticism. In this assay the DNA-PEI-transferrin complexes are subjected to harsh treatments such as being heating to 95 °C and being exposed to ethanol. These treatments are sufficient to cause decomplexation of PEI from DNA, rendering free PEI, which would react with the ninhydrin reagent. Therefore, the quantitative assessment of total free primary amines or loss thereof upon PEGylation by ninhydrin assay is subjective and not quantifiable. Since Ogris' entire set up of the PEG reaction for calculation of the mPEG:PEI molar ratio and assumption of the degree of PEGylation is based on this unconventional assay and has no supporting data, the feasibility of the synthesis method and validity of the product composition claim is questionable.

In comparison, the lipopolymer of the current application is synthesized by reacting the m-PEG reagent to free or unbound PEI whereby the primary amines are maximally accessible to the

PEG reagent and are accurately quantifiable by NMR. The chemical structure and the degree of PEG incorporation in the PEGylated lipopolymer of the present application is fully characterized by a conventional and recognized method (See NMR spectra in Figs. 2,3). Furthermore, the feasibility of the teachings of the present invention is demonstrated with different molecular weights of PEI (MW 1800, 25000) and mPEG(MW 330, 1000). In each case the reaction yields a fully characterized product. The cited references, even when combined, still do not teach or suggest the presently claimed lipopolymer.

In fact, Orgis discourages direct PEGylation of PEI (as in the present application) with the concern that it may adversely affect the DNA condensation process (Orgis et al., page 595, first paragraph under Results section). This shows that Orgis teaches away from the synthesis scheme employed in the present invention. The results show that PEI conjugation to PEG as described in the present application does not affect the DNA condensation process. The gel retardation data in Figure 4 illustrates similar DNA condensation by PEGylated (lane E-H) and non-PEGylated (lane B-D) lipopolymers at different N/P ratios.

Goodbey et al., teaches that the covalent attachment of PEG to PEI reduces binding to serum proteins and enhances stability to salt. They do not teach covalent attachment of PEG to cholesterol- or targeted ligand-linked linked PEI and its benefit for *in vivo* DNA delivery, which is described in this application.

Therefore, neither of the cited references or a combination thereof discloses or suggests lipopolymers comprised of polyethylenimine (PEI), a lipid and a biocompatible hydrophilic polymer, wherein the lipid and the biocompatible hydrophilic polymer are directly and independently attached to the PEI backbone by a covalent bond. Therefore, the Applicants respectfully submit that the

Examiner has failed to establish a case of *prima facie* obviousness and that Claim 12 is allowable and all the claims dependent thereon are also allowable. To that end, the Examiner is requested to withdraw the rejection and allow all pending claims.

The present invention does not broadly claim on the PEI PEGylation and its subsequent impact on DNA delivery. Instead, the present invention is directed to a specific novel lipopolymer composition for DNA delivery and the novelty is due to the presence of a membrane interacting agent (cholesterol or/and targeting ligands) and a PEG group on a single backbone polymer (PEI).

Double Patenting

Claims 1-21 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over the claims of U.S. Patent No. 6,696,038. Claims 22-27 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over the claims of U.S. Patent No. 6,696,038 in view of Epand. A terminal disclaimer is attached to overcome this rejection. The present application and U.S. Patent No. 6,696,038 are commonly owned.

CONCLUSION

In light of the above, the Applicants respectfully submit that all pending claims are now in condition for allowance. Therefore, the Applicants request that the rejections be withdrawn, and that the claims be allowed and passed to issue. If any impediment to the allowance of these claims remains after entry of this Amendment, the Examiner is strongly encouraged to call Dr. Weili Cheng, or in her absence, the undersigned M. Wayne Western, at (801) 566-6633 so that such matters may be resolved as expeditiously as possible.

The Commissioner is hereby authorized to charge any additional fee or to credit any overpayment in connection with this Amendment to Deposit Account No. 20-0100.

DATED this 7th day of September, 2006.

Respectfully submitted,

M. Wayne Western
Registration No. 22,788

Weili Cheng, Ph.D
Registration No. 44,609

THORPE, NORTH & WESTERN, L.L.P.
P.O. Box 1219
Sandy, Utah 84091-1219
Telephone: (801) 566-6633